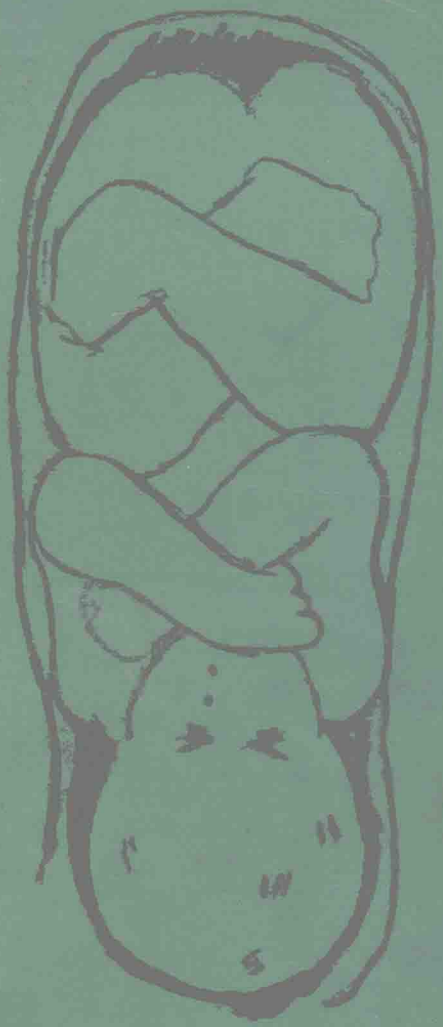


BECK'S OBSTETRICAL PRACTICE AND FETAL MEDICINE

E. STEWART TAYLOR, M.D.

TENTH EDITION

BECK'S
OBSTETRICAL PRACTICE and FETAL MEDICINE

Tenth Edition

E. STEWART TAYLOR, M.D.

Professor and Chairman,
Department of Obstetrics and Gynecology,
University of Colorado School of Medicine, Denver, Colorado

The Williams & Wilkins Company
Baltimore/1976

First Edition, 1935
Second Edition, 1939
Third Edition, 1942
Fourth Edition, 1947
Fifth Edition, 1951
Sixth Edition, 1955
Seventh Edition, 1958
Eighth Edition, 1966
Ninth Edition, 1971

Portuguese Edition, 1940
Spanish Edition, 1947
Second Spanish Edition, 1968
Third Spanish Edition, 1973

Made in the United States of America

Library of Congress Cataloging in Publication Data

Beck, Alfred Charles, 1885–
Beck's obstetrical practice and fetal medicine.

First-9th ed. published in 1935–1971 under title: Obstetrical practice.
Includes bibliographies and index.
1. Obstetrics. 2. Fetus. I. Taylor, Edward Stewart, 1911– II. Title. III. Title: Obstetrical practice and fetal medicine. [DNLM: 1. Fetus. 2. Obstetrics. WQ100 B3930]
RG524.B4 1976 618.2 75-35798
ISBN 0-683-08123-3

Composed and printed at the
WAVERLY PRESS, INC.
Mt. Royal and Guilford Aves.
Baltimore, Md. 21202, U.S.A.

preface to the tenth edition

The scope of the Tenth Edition of *Beck's Obstetrical Practice* has been enlarged to contain a section of *Fetal Medicine*. This is appropriate because Dr. Alfred C. Beck was one of the first obstetricians to focus attention on the newborn infant in cooperation with pediatricians so as to improve neonatal survival rates. Secondly, the University of Colorado Medical Center and its Department of Obstetrics and Gynecology were the first to establish a Division of Perinatal Medicine as a combined unit with the Department of Pediatrics. This creation of a Division of Perinatal Medicine formalized cooperative activities between the Department of Obstetrics and Gynecology and the Department of Pediatrics which has been continuous for thirty years. Fetal medicine as practiced by our obstetricians and the intensive care of newborn infants by our perinatologists have improved perinatal survival rates dramatically in the past three decades.

This text contains a modern section on Fetal Medicine which is subdivided into Physiology of the Fetus, Maternal Health as it Effects Fetal Growth and Development, Effects of Drugs on the Fetus, The High Risk Fetus, Premature Rupture of the Membranes, Evaluation of Growth and Maturity of the Fetus, and Fetal Monitoring during Labor.

During the past five years ultrasonographic techniques, amniotic fluid analyses, and estriol determinations have become essential elements of prenatal care for many patients. Prenatal genetic amniocenteses studies are required for selected patients. The importance and the details of these procedures are covered in Chapters 6 and 47.

All chapters have been revised. Those of particular change are "The Placenta," "Physiology of Pregnancy," "Medical and Surgical Complication of Pregnancy," "Placenta Previa and Abruptio Placentae," Puerperal Infection," "Interruption of Pregnancy," "Cesarean Section," "Control of Conception," and "Clinical Genetics."

The text provides the students, the resident in training, and the obstetrician with essential information for modern obstetrical practice. The bibliography of each chapter has been revised but the classic references have been retained.

I wish to thank my colleagues in the Department of Obstetrics and Gynecology for establishing a high standard of obstetrical practice and for making suggestions for subject matter to include in the text. Drs. Edgar L. Makowski, Dwain D. Hagerman, Watson A. Bowes, Jr., William Droegemueller, and Richard P. Perkins have been particularly helpful. I wish to thank my wife for reading the manuscript and Mrs. Mildred O'Brien for aid in preparation of the text. My appreciation is extended to the publishers for their help.

E. Stewart Taylor, M.D.

contents

Chapter 1

THE OVARIAN CYCLE

Development of the Ovaries

The embryonic ovaries develop from the celomic epithelium on the ventromesial surface of each mesonephros as the underlying mesenchyme becomes altered. The cells proliferate rapidly and give rise to a closely packed, thickened epithelium and a marked condensation of the underlying mesenchyme. The germ cells of the primordial mesenchyme which migrate from the vicinity of the yolk sac undergo rapid division. As this compact mass enlarges, it becomes elevated and projects into the body cavity. These altered portions of the mesonephroi are the anlagen of the sex glands and are termed the genital ridges (Fig. 1.1). In the female the middle third of each ultimately becomes an ovary.

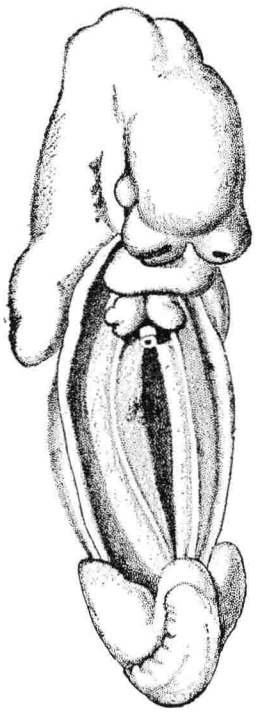
The three major components of the ovary are the germ cells, the cortex and the medulla. The germ cells are recognizable in the 4-week-old human embryo. During the 5th week of embryonic life, the germ cells are found to migrate to the site of the primordial gonad. These germ cells are the source of the ova. The cortex is the second component of specialized ovarian tissue, and it arises from the median portion of the mesonephric body. The cortex produces the follicular cells of the primitive gonad which later become the granulosa cells of the ovary. Ovogenesis and estrogen secretion from the mature ovary both originate in the cortex. The medullary structure of the ovary also rises from the medial mesonephric surface, and the primitive adrenal cortex arises from this same general area. In the male the medulla differentiates into the rete tubules, the efferent ductules, and the seminal structures. The ovarian and testicular androgens are secreted from medullary structures of the adult ovary. The interstitial cells of the testis are medullary derivatives. Rudimentary testicular elements are often found in the medullary portion of the human ovary.

It is through genetic determination that the cortical and medullary gonadal primordia differentiate into testis or ovary. If the embryo has XX sex chromosomoes, the primitive gonad will develop as an ovary. If the embryo has XY sex chromosomes, the primitive gonad will develop as a testis. In the female embryo, the cortical function of the gonads predominates, whereas, in the male embryo, medullary function and structure predominate.

Continued proliferation of the celomic epithelium leads to the formation of a thick outer cellular layer which is continuous with the cell cords, the deeper regions of which contain numerous primitive sex cells. These sex cells eventually are to be encapsulated by the granulosa cells which are derived from the epithelium. The outer cellular layer of the embryonic ovary grows in thickness for a relatively long time and is characterized by multiplication and enlargement of the pregranulosa cells, together with proliferation and reduction in size of the sex cells. In its superficial portion the pregranulosa cells are diffusely placed; more deeply, they occur in clusters and are skirted by mesenchymal cells (Fig. 1.2). These clumps correspond to the outer ends of the seminiferous tubules. Only in the rete region, however, is the former cordlike arrangement of cells discernible.

Fetal stromal cells from the mesenchyme of the mesonephros enter the primitive gonad and surround the blood vessels and rete tubules. Later they extend into the medulla and from there send septa outward to the cortex, dividing it into numerous islands or thick strands, the so-called

pfluger tubules (Fig. 1.3). These strands are evident in the superficial parts of the ovary but become attenuated in the deeper regions, leaving only very slender cordlike groups in the medulla. As the stroma advances, the primitive sex cells become surrounded by the pregranulosa cells to form primitive graafian follicles which then acquire a capsule of stromal cells from the advancing connective tissue elements.



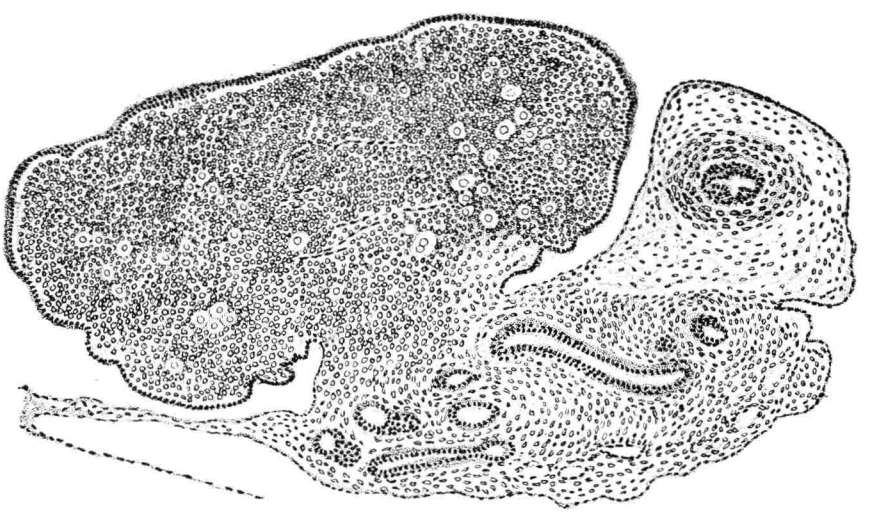
1.1. Embryo at 5 weeks showing the genital ridge on each mesonephros (Bumm).

The female embryo at the 5th to 7th weeks of life can be demonstrated to possess sex chromatin bodies in the cytoplasm before any other evidence of gonadal sex differentiation can be found. After the 7th week, serial section microscopic studies of a human embryo will permit recognition of sex by other means. From the 8th to 10th weeks of embryonic life, the ovary undergoes ovogonial multiplication. Later, ovogonia are converted to oocytes. After the 20th week of embryonic life there is no further increase in germ cells. From the 20th to the 38th weeks of fetal life, the ovary develops its albuginea, and the primordial follicles with their granulosa cells differentiate.

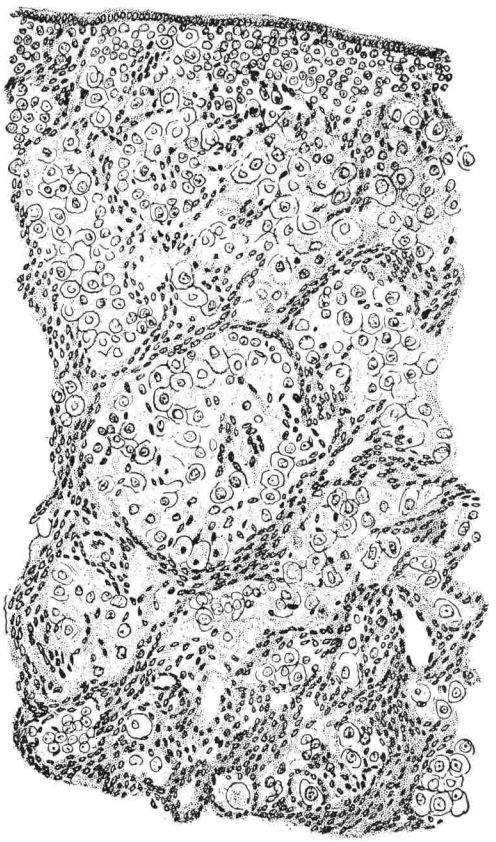
Development of the Follicle

The ovarian follicles of the newborn and preadolescent child are dormant and consist of primitive oocytes surrounded by single layers of flat epithelial cells (Fig. 1.4). Such follicles are present in great numbers at birth and throughout the reproductive period.

During the reproductive age, ordinarily one follicle each monthly cycle is stimulated by the follicle-ripening hormone from the hypophysis. The dormant follicle



1.2. Section of an ovary from a 50-mm fetus (Keibel and Mall)

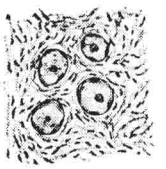


1.3. Section of an ovary from an 80-mm fetus, showing epithelial islands formed by the invasion of connective tissue trabeculae. (Keibel and Mall).

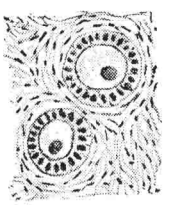
becomes active and in about 2 weeks reaches maturity. The flattened peripheral cells become cuboidal and proliferate to several times their original number to form a single layer of cuboidal cells that line the follicle. This is the first stage in the development of the membrana granulosa. The primitive oocyte likewise increases in size and its nucleus is considerably enlarged (Fig. 1.5). Proliferation continues and within a short time several layers of closely packed, polyhedral granulosa cells are seen in the place of the original one. A thin clear zone, the zona pellucida, appears on the inner margin of these cells and surrounds the oocyte. Coincidently, the connective tissue adjacent to the follicle is arranged in a circular manner (Fig. 1.6).

Further proliferation of the membrana granulosa results in rapid growth of the follicle. Soon, spaces are observed between groups of cells, and in these liquor folliculi accumulates, follicular fluid containing the ovarian estrogenic hormone. Small vessels appear in the connective tissue surrounding the granulosa layer and vascularize this tunic (Fig. 1.7).

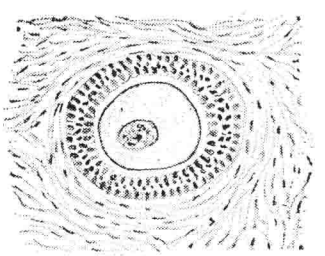
Coalescence of the fluid-filled spaces leads to a lateral displacement of the



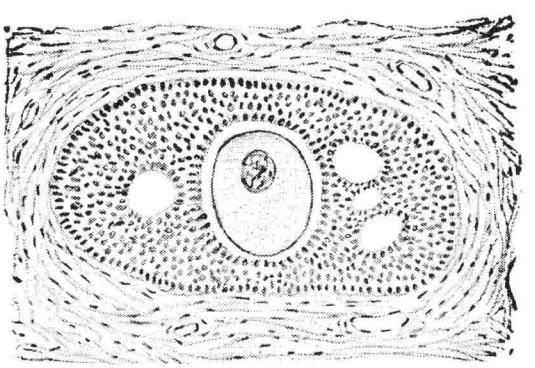
1.4. Dormant follicles



1.5. Beginning follicular development



1.6. Enlarging oocyte, zona pellucida, proliferating stratum granulosum, early tunica interna.

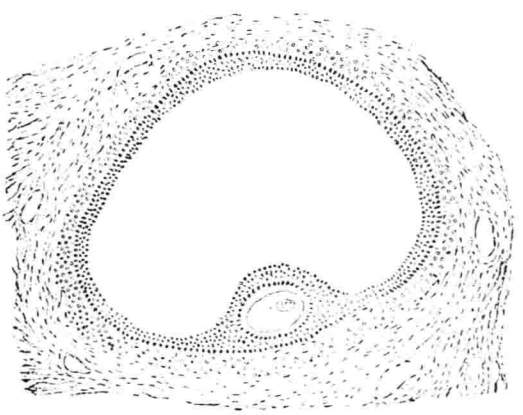


1.7. Vacuolization of granulosa layer. Vascularization of tunica interna. Figures 1.4–1.7 are of the same magnification. Note the progressive enlargement of the follicle, the oocyte, and its nucleus.

oocyte and its surrounding cells, thus forming the germ hill (cumulus or discus proligerus). The granulosa cells are large and polyhedral, except those about the oocyte and in the basal layer next to the connective tissue theca, where they are somewhat columnar and radially arranged. As the vascularization of the connective tissue tunic increases, its cells proliferate and arrange themselves into two layers. Those in the tunica interna grow considerably larger, become epithelioid in character, and are filled with fat globules which contain a yellow pigment. The presence of this pigment has led to their being termed theca lutein cells. The outer layer, tunica externa, resembles the connective tissue of the ovarian stroma, but is circularly arranged. Enlargement of the oocyte continues as it is preparing for the splitting off of the first polar body (Fig. 1.8).

Up to the time of puberty, the follicles develop in the deeper portions of the ovarian cortex. They never reach the surface and consequently fail to rupture. Sooner or later, retrogressive changes take place. Degeneration and fragmentation of the oocyte occur with absorption of the fragments by phagocytic cells derived from the granulosa elements. Rapid destruction of the granulosa cells follows. The theca cells proliferate, lose some of their epithelioid character, and revert to the fibroblastic type to form dense fibers which convert the former follicles into an atretic follicle.

Even after puberty, many follicles terminate in the manner described. After puberty, however, some of them develop near the surface of the cortex. As a follicle matures, it is forced toward the periphery. The tissue intervening between the follicle and the surface becomes thinner and, deprived of its circulation, atrophies. The thin outer wall then ruptures and the ovum is extruded.

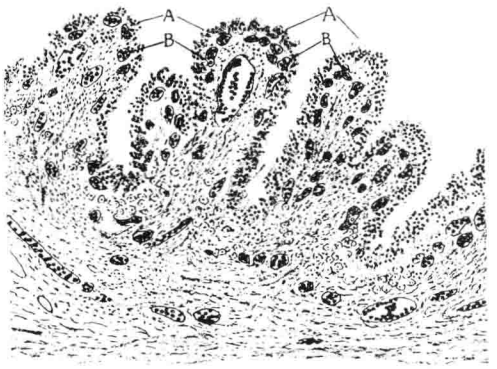


1.8. Well developed follicle with discus proligerus and changed theca interna. The magnification is 2/3 that of the preceeding figures.

Development of Corpus Luteum

Following rupture of the follicle and expulsion of the ovum, a corpus luteum is formed under the influence of the luteinizing hormone from the anterior lobe of the hypophysis. The life history of the corpus luteum has been divided into four stages: hyperemia, vascularization, maturity, and retrogression. These stages in the rapid development of this important structure, however, merge with each other as the histologic picture changes from day to day. In fact, the progressive steps in the development of the corpus luteum are so characteristic that the experienced observer can estimate its age to within 1 or 2 days from its microscopic appearance. After the ovum and liquor folliculi are expelled, the cavity of the follicle shrinks and its walls are thrown into folds. The site of rupture is closed by fibrin which soon becomes organized into a scar. Although the cumulus cells which surround the ovum are cast off at the time of ovulation, most of the granulosa layer is retained. The cells of this layer, however, are still without blood vessels and receive their nourishment from the underlying theca. Extreme hyperemia is present in the theca interna, the engorged vessels of which form a vascular zone beneath the granulosa layer. The theca cells grow much larger, become polyhedral, and fill with lipoid material as the changes observed prior to ovulation continue (Fig. 1.9.).

Within 24 hours after the follicle ruptures, capillaries from the adjacent theca penetrate the granulosa layer and in a few days reach the central cavity. In the substance of this layer they form a network which, by the 6th day, makes contact with practically every granulosa cell. The abundantly nourished granulosa cells become greatly enlarged and more closely packed



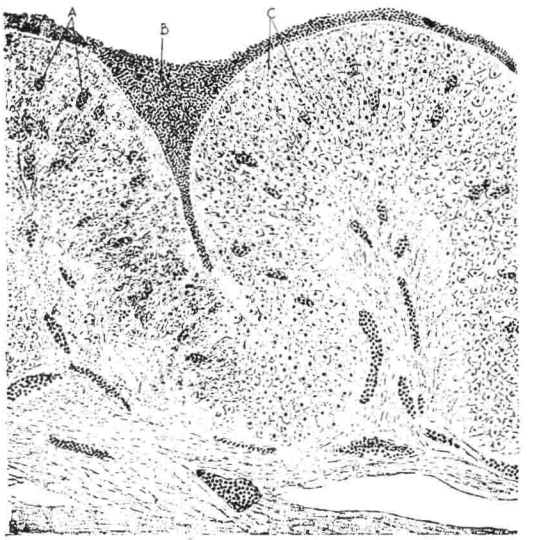
1.9. Corpus luteum—very early—hyperemia. Folds in the wall of the collapsed follicle. Thin granulosa layer (*A*) internal to the vascular zone of the theca interna (*B*).

as their size increases. Connective tissue invades the granulosa lutein layer along with the capillaries and on reaching the central cavity forms a limiting membrane between the latter and the lutein cells. The greatly hypertrophied granulosa lutein layer is thus separated from the central cavity and divided into numerous zones by the invasion of connective tissue and blood vessels from the theca interna. The cells of the latter, having given up their nutriment to the granulosa elements, grow smaller and resemble the earlier theca cells (Figs. 1.10 and 1.11).

The newly formed vessels in the lutein layer are tortuous and distended with blood for about 8–10 days. Subsequently they become straight and narrow, containing relatively little blood, since the endothelial nuclei of the collapsed capillaries are packed more densely than previously around the lutein cells. This observation has led to the suggestion that the functional activity of the corpus luteum is limited largely to the first 8–10 days of its life if pregnancy does not occur. The subsequent behavior of the endometrium seems to lend support to such a suggestion as does the observation that the increasing phospholipid content (an index of functional activity) of the corpus luteum parallels the period of engorgement.

If pregnancy occurs, the engorgement of the capillaries continues and the life of the corpus luteum is prolonged (see "Ovaries" in Chapter 7, "Physiology of Pregnancy").

If pregnancy does not occur, evidence of retrogression appears in the lutein cells soon after the engorgement of the capillaries ceases. Several days before the onset of menstruation, fat deposits are observed



1.10. Corpus luteum—vascularization. Vessels entering the granulosa layer (*A*); hemorrhage into the lumen (*B*); granulosa cells increased in number and size, and containing lutein (*C*); theca cells smaller and less prominent.

1.11. Corpus luteum—late stage. Lutein layer convoluted. Connective tissue trabeculae passing through lutein layer to the limiting membrane between the lutein elements and the blood in the lumen.

in the granulosa lutein layer. Soon thereafter, the volume of this tissue is markedly diminished because of shrinkage and collapse of many of the cells, which stain poorly, lose some of their pigment, and are laden with fat. Some of the cells remain large and are heavily vacuolated while others are greatly shrunken. The diversity of cell change gives the lutein layer a characteristic appearance in the stage of retrogression. Ultimately, this layer is converted into a shrunken, convoluted hyalinized zone surrounding the core of connective tissue which develops from the thickened limiting membrane and fills the central cavity. The retrogressed corpus luteum is then known as a corpus albicans (Fig. 1.12).

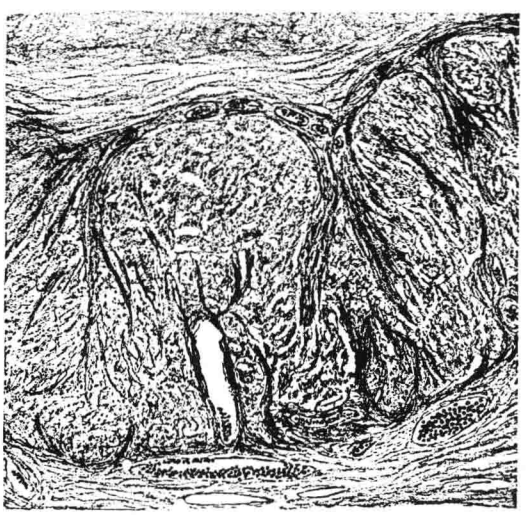
In Figure 1.13 the various stages in the development and retrogression of the corpus luteum are shown graphically.

Hormones of the Ovary

The ovary secretes estrogens, progesterone, androgens, and perhaps relaxin, a polypeptide hormone. The significance of relaxin in the human subject is not known and presently has no clinical importance.

Estrogens

Allen and Doisy described concentrates of an estrogen identified by their bioassay test in 1923, and in 1929 Butenandt and Allen and Doisy independently announced the identification of the first pure estrogen, estrone. This work followed earlier biologic experiments by Knauer (ovarian transplants, 1900) and Ascheim and Zondek who showed that urine from pregnant women contained large amounts of estrogen. Estriol was isolated from urine by Marrian in 1930, and MacCorquodale crystallized the most potent of the natural estrogens, estradiol-17β, from ovarian follicular fluid in 1936.



1.12. Corpus luteum—retrogression. Lutein layer becomes hyalinized as the cells lose their pigment and shrink. Limiting membrane grows thicker and gradual organization takes place.

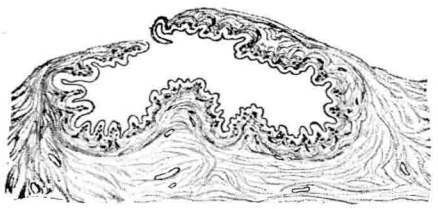
Estrogens are lipid compounds and have the tetracyclic hydrocarbon nucleus of the other steroidal hormones. The estrogens are distinguished from the other steroids by having a phenolic ring A. The formulas for estradiol-17β, estrone, and estriol are given in Figure 1.14.

Synthetic chemicals with estrogenic activity have been prepared. The first of these appeared in 1938, introduced by Dodds and others, and is called diethylstilbestrol.

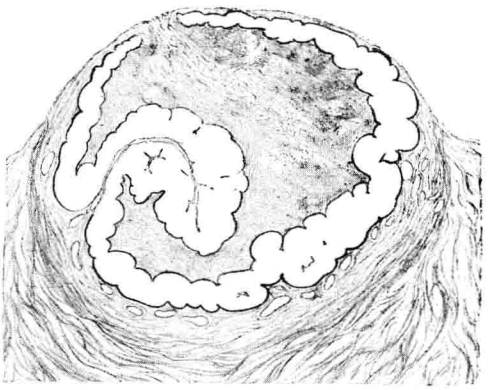
Hexestrol and dienestrol are other synthetic compounds with estrogenic activity that have been introduced since the discovery of diethylstilbestrol. In addition to the synthetic chemicals with estrogenic activity, estrogenic compounds similar to the natural occurring substances have been prepared. The main representatives of the synthesized estrogens are the 17α-ethinyl steroids.

Estrone and estradiol-17β are the main estrogens that may be isolated from ovarian tissue and follicular fluid. The human ovary is able to synthesize estrone and estradiol-17β from acetate, cholesterol, progesterone, and androstenedione. Excreted urinary estrogen is approximately 10% estradiol-17β, 30% estrone, and 60% estriol. The significance of urinary levels of the various estrogen fractions during the normal menstrual cycle cannot be stated with certainty. The remaining portions of estrogens not excreted in the urine are either converted to some other compound in the body or are eliminated in the feces and bile.

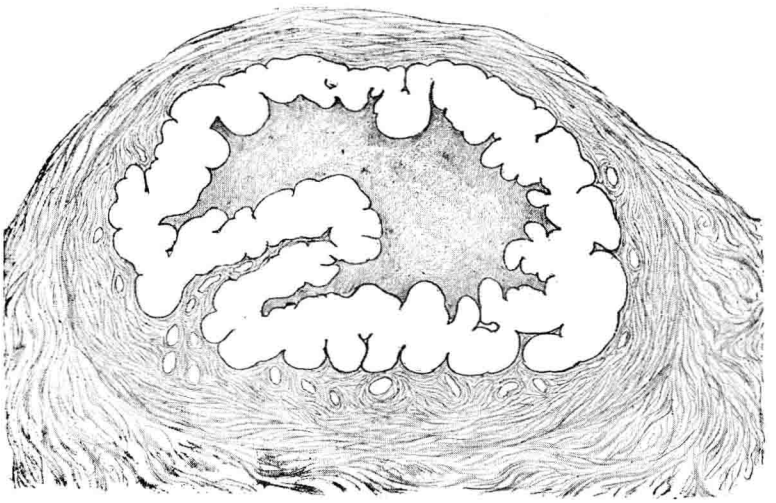
The theca interna cells of the ovary produce estrogens. Estradiol-17β and estrone are the most biologically active of the estrogenic elements of the human ovary.



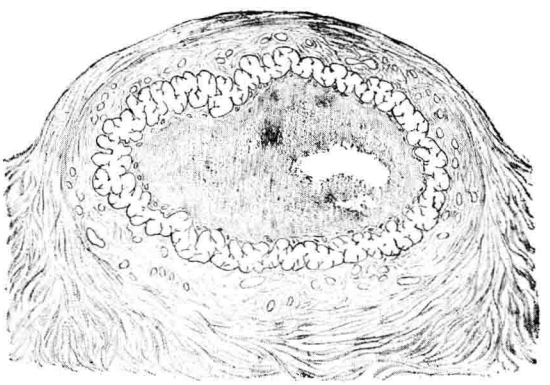
A



B



C



D

1.13. Various stages in the development of the corpus luteum

(*A*) Early stage. Collapsed follicle with a folding of its walls. Granulosa layer proliferating but thin.

(*B*) Vascularization. Hemorrhage into the lumen. Site of rupture closed by fibrin which is becoming organized. Granulosa cells increased in number and size to form well-developed lutein layer.

(*C*) Late stage. Lutein layer greatly thickened and convoluted.

(*D*) Retrogression. Lutein layer shrinking and losing its pigment. Limiting membrane between it and the blood clot in the lumen increasing in size and participating in the gradual organization of the corpus luteum.

1.14. Estrogens

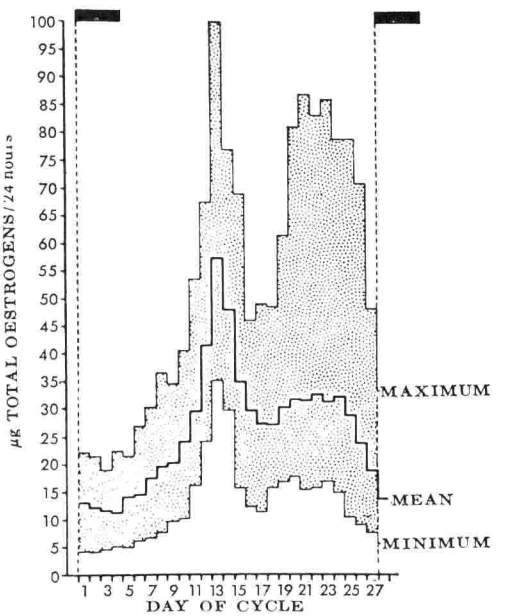
Estriol, although biologically active, is mildly active as compared to estradiol-17β or estrone. There are several other estrogenic compounds found in human secretions whose exact significance is not known. These are 2-methoxy-estrone, 18-hydroxyestrone, 6-hydroxyestrone, 16-epiestriol, 2-methoxyestriol, 16-oxoestradiol-17β, 16-oxoestrone, 16α-hydroxyestrone, 16β-hydroxyestrone, 11β-hydroxyestradiol-17β, equilenin, and estranediol.

The amounts of estriol, estrone, and estradiol-17β found in the urine during normal menstrual cycles of normal women are given in Figure 1.15. Although there are wide variations in normal subjects, it can be seen that the amount of each of the three principal estrogenic fractions found during the menstrual cycle is relatively small at menstruation and gradually increases to a maximum peak at the 13th day of the cycle. After ovulation, a fall in all the urinary fractions occurs, with a slight secondary rise at around the 21st or 22nd day of the cycle. This secondary rise probably represents corpus luteum maturity. Just before menstruation the amount of each of the hormone metabolites in the urine falls off considerably. The level of urinary estriol, during days 1–5 of a normal menstrual cycle, is approximately 5 μg in a 24-hour period. This level begins to rise with maturation of the graafian follicle to a peak of 35–50 μg per 24 hours of urinary excretion at the time of ovulation. After follicular rupture, the 24-hour excretion of estriol in the urine falls to about 15 μg. Around days 21–22 of the normal menstrual cycle, estriol in the urine is found to be approximately 20 μg in a 24-hour period. Just before menstruation, the expected level is 10 μg per day.

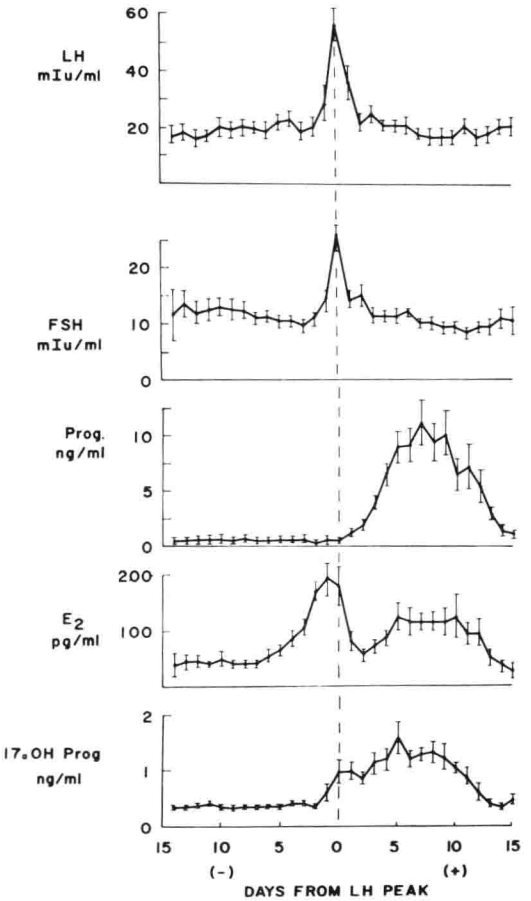
The urinary excretion of estrone and estradiol-17β follows a similar pattern (Fig. 1.15), except that the amounts of each of these compounds are much less than those of estriol.

Modern methods of analysis reveal that the concentrations of the estrogens in the blood vary during the menstrual cycle in a pattern not unlike that found in urine (Fig. 1.16). This data does not show the common preovulatory surge of estrone which probably triggers the pituitary midcycle luteinizing hormone peak or surge which is responsible for ovulation.

Perfusion experiments by Rabinowitz and by Smith and Ryan have demonstrated that the human ovary can convert labeled acetate to estrone and estradiol-17β. Cholesterol can be transformed by the human ovary to estrone. The ovary can also convert progesterone to estrone, and androstenedione and testosterone to estrone. Figure 1.17 demonstrates the pathways of steroid synthesis in the human ovary.



1.15. Mean, maximum, and minimum levels of total urinary oestrogens from 16 women, aged 18 to 45 years, with normal menstrual cycles. Time between onset of bleeding (day 1) and ovulatory peak of estrone/estradiol varied from 10 to 18 days (mean 13 days), and between estrone/estradiol ovulatory peak and first day of next menstruation, from 12 to 16 days (mean 14 days). Curves were constructed by superimposing individual curves in such a way that each of the estrone/estradiol ovulatory peaks coincide with day 13 of the composite curves. (■ = Menstruation) (From J. B. Brown, R. Kellar, and G. D. Matthew: Journal of Obstetrics and Gynaecology of the British Empire, *66:* 177, 1959.)



1.16. Mean values of LH, FSH, progesterone (*Prog.*) estradiol (E_2) and 17-hydroxyprogesterone (17 *αOH Prog.*) in daily serum samples of 9 women during ovulatory menstrual cycles. Data from different cycles combined with the use of the day of the midcycle LH peak as the reference day (*Day 0*). The *vertical bars* represent 1 standard error of the mean. (From I. H. Thorneycroft et al.: American Journal of Obstetrics and Gynecology, 111: 947, 1971.)

Progesterone

Progesterone arises from the granulosa lutein cells or from the theca lutein cells of the corpus luteum. Progesterone is synthesized by the human ovary from acetate, cholesterol, and pregnenolone. An increase in plasma progesterone occurs a few hours after ovulation takes place (Fig. 1.16).

In 1910 Fraenkel demonstrated that the corpus luteum was necessary for implantation and maintenance of the rabbit's pregnancy. A progestational substance was isolated from the sow's ovary in 1929 by Corner and Allen. It was Butenandt who identified the corpus luteum hormone as a steroid. Pregnanediol was discovered as a urinary excretory product by Butenandt in 1930. It was not until 1937, however, that Venning and Browne demonstrated the relationship between injected progesterone and urinary pregnanediol.

The chemical formulas for progesterone and pregnanediol are given in Figure 1.18. Approximately 70–75% of experimentally injected progesterone can be accounted for in the urine when tracer studies are used.

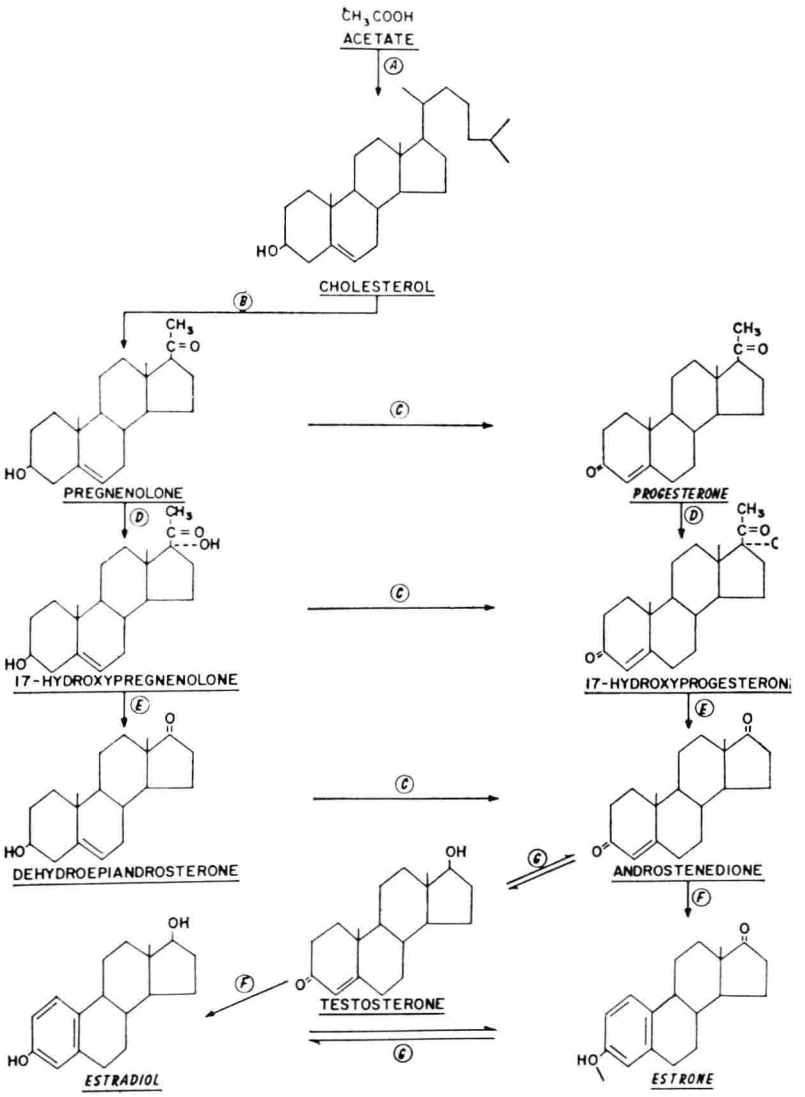
Thorneycroft and others have found that serum progesterone levels in the normal menstrual cycle are less than 1 ng per ml until near the middle of the cycle. Starting at the peak of the luteinizing hormone (LH) level, serum progesterone begins to rise and reaches its highest level 5–6 days after the height of the LH surge. Thereafter, serum progesterone levels gradually fall during the luteal phase of the cycle until just before menstruation when the levels become equivalent to those in the preovulatory part of the cycle (Fig. 1.16).

Approximately 3 mg of progesterone is secreted by the ovaries and the adrenal gland by the normal adult woman per 24-hour period during the follicular phase of the cycle. During the luteal phase approximately 22 mg of progesterone is secreted by the glands. These secretion rates have been calculated by Little and others.

Hypothalamic and Pituitary Regulation of the Ovary

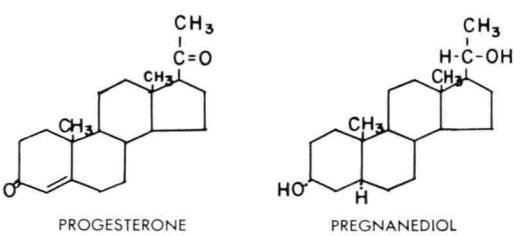
Polypeptides called releasing hormones are made in the hypothalamus and reach the pituitary by its portal circulation. Presently established hypothalamic hormones are thyrotropin releasing hormone (TRH), corticotropin releasing hormone (CRH), luteinizing hormone releasing hormone (LHRH) (which may also effect follicle stimulating hormone release), and somatostatin or growth hormone release inhibiting hormone. Prolactin secretion is also regulated by an inhibiting hormone from the hypothalamus which may be identical to TRH.

Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are the pituitary hormones directly concerned with follicu-



1.17. Pathway of steroid biosynthesis in the ovary. A, formation of sterol from acetate; *B*, cleavage of cholesterol side chain—converts C_{27} to C_{21} compound; *C*, 3β-ol-dehydrogenase and Δ^4-Δ^5-isomerase reaction; *D*, 17α-hydroxylation; *E*, cleavage of side chain—converts C_{21} to C_{19} compounds; *F*, aromatizing reaction; *G*, 17β-ol-dehydrogenases (reversible). (From O. W. Smith and K. J. Ryan: American Journal of Obstetrics Gynecology, *84:* 141, 1962.)

lar growth and ovulation. Li and others isolated and purified FSH in 1949. Bahn, Lorenz, Bennett, and Albert in 1953 demonstrated that the human anterior pituitary gland possesses FSH. In 1958 Gemzell and others recovered purified FSH and LH from human pituitary glands and used this material to induce ovulation in patients who were not ovulating spontaneously. Fe-



1.18. Progesterone and pregnanediol

vold, Hisaw, and Leonard had previously demonstrated FSH and LH stimulation of gonadal tissue (1931).

FSH stimulates maturation of the ovarian follicle and is excreted in the urine as a complex protein. The metabolic pathways of FSH are not entirely understood. The hypothalamus, pituitary, and ovary interact to cause ovulation. A small increase in estrogen concentration in the blood to a critical level results from the growth of a selected follicle under stimulation from FSH. The increased level of estrogen in the blood stimulates hypothalamic LHRH which in turn causes the LH peak (Fig. 1.16). Ovulation occurs shortly after the LH surge; the follicle luteinizes, progesterone is synthesized, its concentration in blood increases, and the basal body temperature rises. If fertilization of the released ovum does not occur, luteolysis takes place; the mechanism of regulation of this phenomenon is unknown.

LH and FSH are found in the serum of children and of men. The concentrations of LH and FSH increase after age 10. There is a sharp rise in serum FSH after the menopause. Neither FSH or LH alone can initiate ovulation.

REFERENCES

Development of Ovaries, Follicle, and Corpus Luteum

Brewer, J. I.: Studies of the human corpus luteum. Am. J. Obstet. Gynecol., *44:* 1048, 1942.

Corner, G. W.: Development, organization and breakdown of the corpus luteum in the rhesus monkey. Contrib. Embryol., Carnegie Inst., *31:* 117, 1945.

Crosby, W. M., and Hill, E. C.: Embryology of the müllerian duct system; review of present-day theory. Obstet. Gynecol., *20:* 507, 1962.

de Graaf, R.: *De mulierum organis generationi inservientibus*, p. 165. Ludvni., Batav., 1677. *De testibus mulieribus sive ovariis*, p. 292, Ludvni., Batav., 1677.

Dempsey, E. W., and Bassett, D. L.: Observations on the fluorescence, birefringence and histochemistry of the rat ovary during the reproductive cycle. Endocrinology, *33:* 384, 1943.

Gillman, J.: The development of the gonads in man. Contribut. Embryol., Carnegie Inst., *32:* 81, 1948.

Meyer, R.: Über Corpus luteum-Bildung beim Menschen. Arch. Gynaekol., *93:* 354, 1911.

Schroeder, R.: Über die zeitlichen Beziehungen der Ovulation und Menstruation. Arch. Gynaekol., *101:* 1, 1913.

Strassmann, E. O.: The theca cone and its tropism toward the ovarian surface, a typical feature of growing human and mammalian follicles. Am. J. Obstet. Gynecol., *41:* 363, 1941.

von Baer, C. E.: *De ovi mammalium et hominis genesi*. L. Voss, Leipzig, 1927.

Waldeyer, H.: *Eierstock und Ei*. W. Engelman, Leipzig, 1870.

White, R. F., Hertig, A. T., Rock, J., and Adams, E.: Histological and histochemical observations on the corpus luteum of human pregnancy. Contrib. Embryol., Carnegie Inst., *34:* 55, 1951.

Witschi, E.: Migration of the germ cell of human embryos from the yolk sac to the primitive gonadal folds. Contrib. Embryol., Carnegie Inst., *32:* 67, 1948.

Witschi, E.: Embryology of ovary. In *The Ovary*, edited by H. G. Grady and D. E. Smith, Ch. 1, p. 4. Williams & Wilkins Co., Baltimore, 1963.

Estrogens

Adler, L.: Zur physiologie und pathologie der ovarial funktion. Arch. Gynaekol., *95:* 349, 1912.

Allen, E., and Doisy, E. A.: Ovarian hormone J. A. M. A., *81:* 819, 1923.

Aschheim, S., and Zondek, B.: Hypophysenvorderlappenhormon und ovarialhormon im harn von schwangeren. Klin. Wochenschr., *6:* 1322, 1927.

Brown, J. B.: The relationship between urinary oestrogens and oestrogens produced in the body. J. Endocrinol., *16:* 202, 1957.

Brown, J. B.: The metabolism of oestrogens and the measurement of the excretory products in the urine. J. Obstet. Gynaecol. Br. Emp., *66:* 795, 1959.

Butenandt, A.: Über "Progynon" ein krystallisiertes weibliches sexualhormon. Naturwissenschaften, *17:* 868, 1929.

Cohen, S. L.: A method for the rapid colorimetric assay of total estrins in pregnancy urine. J. Clin. Endocrinol. Metab., *26:* 994, 1966.

Dodds, E. C., Goldberg, L., Lawson, W., and Robinson, R.: Oestrogenic activity of certain synthetic compounds. Nature, *141:* 247, 1938.

Doisy, E. A., Veler, C. D., and Thayer, S. A.: Folliculin from urine of pregnant women. Am. J. Physiol., *90:* 329, 1929.

Knauer, E.: Die ovarientransplantation. Arch. Gynaekol., *60:* 322, 1900.

MacCorquodale, D. W., Thayer, S. A., and Doisy, E. A.: The isolation of the principal estrogenic substance of liquor folliculi. J. Biol. Chem., *115:* 435, 1936.

Marrian, G. F.: The chemistry of oestrin. I. Preparation from urine and separation from an unidentified solid alcohol. Biochem. J., *23:* 1090, 1929.

Marrian, G. F.: The chemistry of oestrin. An improved method of preparation and the isolation of active crystalline material. Biochem. J. *24:* 435, 1930.

Rabinowitz, J. L.: The biosynthesis of radioactive 17β-estradiol. Arch. Biochem. Biophys., *64:* 285, 1956.

Smith, O. W., and Ryan, K. J.: Estrogens in the human ovary. Am. J. Obstet. Gynecol., *84:* 141, 1962.

Progesterone

Butenandt, A.: Uber das Pregnandiol, einen neuen Sterinabkommling aus Schwangerenham. Ber. Chem. Ges., *63:* 659, 1930.

Corner, G. W., and Allen, W. M.: Physiology of the corpus luteum. Production of a special uterine reaction (progestational proliferation) by extracts of the corpus luteum. Am. J. Physiol., *88:* 326, 1929.

Fraenkel, L.: Die funktion des corpus luteum. Arch. Gynaekol., *68:* 438, 1903.

Fraenkel, L.: Neue experimente zur funktion des corpus luteum. Arch. Gynaekol., *91:* 705, 1910.

Little, B., Tait, J. F., Tait, S. A. S., and Erlenmeyer, F.: The metabolic clearance rate of progesterone in males and ovariectomized females. J. Clin. Invest., *45:* 901, 1961.

Thorneycroft, I. H., Mishell, D. R., Jr., Stone, S. C., Kharma, K. M., and Nakamura, R. M.: The relation of serum 17-hydroxyprogesterone and estradiol-17β levels during the human menstrual cycle. Am. J. Obstet. Gynecol., *111:* 947, 1971.